Meeting Summary
Third National Forum on Biomedical Imaging in Oncology
January 31 - February 1, 2002 — Arlington, Virginia
Co-sponsored by the National Cancer Institute and National Electrical Manufacturers Association

The Fourth National Forum on Biomedical Imaging will take place on February 6-7, 2003 at the Hyatt Regency Bethesda.

Introduction/Objectives [Presentation Slides]
The Third National Forum on Biomedical Imaging in Oncology (NFBIO) convened imaging technology developers, clinical and laboratory investigators in academia and industry together with individuals in key government agencies involved in funding, regulating and reimbursing technology. Speakers focused on the topics of molecular probe development and devices needed to detect molecular probes.

The major theme of this year's Forum was molecular imaging. How can imaging probes and devices be used in the preclinical development and clinical application of screening, prevention, and treatment interventions? A goal of the NFBIO was to facilitate and accelerate the development and clinical evaluation of effectively molecularly targeted interventions. Another goal was to discuss how we can utilize genomics, gene expression and other molecular data to permit current treatments to be targeted to patients most likely to respond which in turn facilitates the development of new and highly effective interventions in prevention, screening and therapeutics.

Industry consolidation is affecting the entire medical imaging device industry. As an example, the Medical Products Department in the National Electrical Manufacturer's Association (NEMA) has decreased from 80 to 36 member companies. However, the ones that remain are considerably larger when compared to the average size of companies several years ago. Overall, the imaging industry continues to grow.

FORUM ISSUES: PROGRESS SINCE LAST YEAR

Food and Drug Administration (FDA)
An overview of the issues surrounding drug, biologic and device products regulated by the FDA was presented. Product jurisdiction is not always clear. There are numerous developmental challenges because definitions and laws regulating these products overlap. A Combination Products Program will be established this year in the Office of the FDA Commissioner and will serve as a focal point. An ombudsman will resolve disputes between the Centers.

Manufacturers were encouraged to consult with the FDA in the early stages of their product's life cycle to discuss the evidence required to show a product is safe and effective. Data from European trials can be submitted to the FDA, but data must meet US standards. FDA guidance for literature submission can be found at http://www.fda.gov/cder/guidance/2853dft.htm .

Centers for Medicare and Medicaid Services (CMS, formerly HCFA)
CMS is working on ways to accelerate technology diffusion that will include:
- providing a more open interactive process
- applying clearer and more consistent standards for decisions
- coordinating coverage, coding and payment decisions
- avoiding duplicative studies already required for FDA approval

The Medicare Coverage Advisory Group has developed a framework for reimbursement for diagnostic tests that makes use of evidence-based medicine in an analytical format for rendering decisions. Decision coverage is based on functional outcomes and quality of life measurements. White papers are being developed. Increased diagnostic capability will not be approved unless associated with an impact on clinical management. The FDG-PET approval process used this newer analytic framework.

National Cancer Institute (NCI) **[Presentation Slides]**
Last year the NCI worked with the FDA, CMS and device manufacturers to launch the Digital Mammography Clinical Trial, and is gearing up to launch the National Lung Screening Trial, which will evaluate spiral CT vs. CXR in individuals at risk for lung cancer. The NCI, FDA and CMS continue to discuss the evaluation of imaging diagnostics. The Interagency Council on Biomedical Imaging in Oncology continues to hold confidential meetings between technology developers, NCI, FDA and CMS. In addition to imaging diagnostics, the NCI is working on ways to expand interagency discussions to include in vitro diagnostics.

MOLECULAR TARGETS: TAKING IMAGING PROBES INTO THE CLINIC

The Needs, Problems and Challenges
Cancer diagnostics, imaging probes and drugs for treatment interventions must proceed down a complex preclinical developmental pathway, and then through a series of clinical development steps. Some of the challenges include:

- deciding on standards for molecular endpoints
- having the technology tools in place for assessment
- information and shared databases available to develop assays, probes and drugs
- adequate funding to support these endeavors
- public interest and willingness to participate in developing the steps

Scientists from different disciplines were encouraged to interact with each other and to focus on clinical issues. How do we achieve interdisciplinary science? Should interdisciplinary centers be created? There is increasing recognition for this in academic centers. Could industry and resource allocation decisions be centered on the development of key biomedical questions? Which brings up the question of what is the business? How risky is it? And is it too long term?

The future of therapy is in combinations of agents and the exception will be single agent treatment. Is FDA poised to respond? Is CMS poised to respond? What types of information will be needed for the decision making process?

Industry Perspective: STI-571 and VEGF
The use of F18-FDG PET imaging of gastrointestinal stromal tumors (GIST) treated with STI/571 (Gleevec) was discussed as an example of the combination of a molecularly targeted agent and imaging for the treatment of cancer. This targeted drug therapy works in cancer by directly inhibiting certain tyrosine kinases. FDG-PET is a very sensitive measure at an early stage of the subsequent response to Gleevec.

Imaging Cell Death in Untreated and Treated Human Tumors With Tc-99m Annexin-V
Apoptosis imaging was presented as a measure of in vivo chemoresponsiveness; tumors not showing apoptosis don't show a response. The agent, Annexin, is targeted at a specific intracellular receptor and has nanomolar affinity to membrane bound phophatidylserine. It is aimed at early detection, tailoring of drug therapy and evaluation of new drugs. Whole body imaging carried to single cell level reveals membrane binding. Preliminary results from a tumor model for murine lymphoma revealed a 50% increase in the amount of apoptosis present/uptake of agent. Annexin has potential in non-Hodgkin's lymphoma, breast cancer and sarcoma. Annexin is well tolerated in a phase I study with breast cancer patients.

NCI Initiatives: Resource for Molecular Imaging Development [Presentation Slides]
NCI initiatives for the development of molecular imaging probes and enhancers:

- DCIDE program for pre-clinical development of promising imaging agents
- Radionuclide Resource at Washington University
- Program announcements for technology development
- Network for Translational Research in Optical Imaging
- Interagency Council on Biomedical Imaging in Oncology, http://www3.cancer.gov/scienceresources/announcements/imaging.html
- National Forum on Biomedical Imaging in Oncology, http://www3.cancer.gov/dctd/forum/
- Other initiatives can be found at http://www3.cancer.gov/bip/initiatives.htm

Panel - Clinical Development: Addressing the Challenges
Angiothelin, a hypothetical compound that may control endothelial proliferation, was portrayed as being in phase I/II clinical trials for cancer and age-related macular degeneration (ARMD). Several questions were raised using this agent as a model:

- Is it appropriate to combine data from cancer and ARMD populations? What about from patients with different tumor types? Which of the potential indications are acceptable and what kind of data will be needed? The FDA would look at data from both trials to evaluate safety and clinical setting to determine if a phase III trial might be more meaningful. Efficacy is more of a concern for payers.
- The length of safety data collection would require follow-up on adverse events as well as therapeutic outcomes. Does the concept of "owning" the patient for the length of the study, common in therapeutics (e.g., following adverse events for two years if two year survival is the endpoint), apply to diagnostics?
- The attention given to safety of tracers is problematic. Tracer has neither physiologic impact nor attributable safety impact, if used at minuscule levels. Complete safety cannot be assumed for diagnostics. For instance, there is a possibility of antibody formation with protein administration.
- Which of the potential indications are acceptable and what kinds of data would be needed? Sponsor may be able to make a clinical claim and prove benefit of imaging angiogenesis by searching the literature. Does the agent give more information than an ordinary CT scan? Does the agent impact the course of treatment?
- What about trials with a diagnostic and therapeutic combination? The FDA suggested looking at adverse events for a diagnostic separate from treatment, if possible.
- Is lack of progression, as opposed to complete response or partial response, a suitable surrogate endpoint for angiogenesis inhibitors, and thus for trials of diagnostic agents intended to evaluate response to them? Evaluation by FDA is done on a case-by-case basis.

Molecular Markers and Magnetic Resonance Imaging (MRI) [Presentation Slides]
Angiogenesis in breast cancer was studied with dynamic contrast enhanced MRI and immunohistochemical markers. The dynamic contrast enhanced MRI results were characterized by vascular volume and permeability. The overall immunohistochemical (IHC) characterization of breast tumors included the following markers: p53, trombospondin-1 (TSP-1), VEGF, microvessel density (MVD) with CD31 and endoglin with CD105, a marker for the neovasculature in a tumor. An overall angiogenic parameter known as the angiogenesis index (AI) was calculated by combining the outcome of p53, TSP-1 and CD-31 measurements. Early results indicate that there is a good correlation between the MVD and endoglin from IHC and vascular volume from MRI as well as the vascular permeability from the MRI and the angiogenesis index from IHC. Since immunohistochemical markers employed in this study have been shown by others to have prognostic importance for breast cancer, it is hoped that MRI studies such as the ones reported here would also have a non-invasive prognostic value.

PRE-CLINICAL DEVELOPMENT OF IMAGING PROBES

Overview of Probe Development: The Steps [Presentation Slides]
A multitude of new targets, better imaging of known targets, the opportunity to speed development of drugs and more accurate assessment were given as reasons for the development of new diagnostic probes. Chemical libraries and the use of animal models will make drug discovery faster and cheaper. Major hurdles for development are:

- deconvolution techniques: sensitivity
- biopanning: applying whole organism to screening
- agonist/antagonist issues of libraries
- cost

Contrast agents were portrayed as "smart", targeted and conventional. Feasible designs could be used in clinical trials. Several barriers emerge when moving from conventional to targeted to "smart' agent development.

Academia and industry were encouraged to develop partnerships for contrast development for established targets, to explore new targets and to determine drug efficacy.

Industry Perspective: Use of Imaging Probes in the Evaluation of Pharmaceuticals – Decision Points in Development [Presentation Slides]
The history of how industry uses imaging for drug development was reviewed. The value of programs with PET imaging were emphasized.

Dual Imaging Probes [Presentation Slides]
Metal chelates are a common thread for developing imaging agents for various imaging devices and are delivered as a result of inherent specificity. Multi-modal imaging agents lead to a cocktail approach, e.g. a metal iron for optical and MR imaging. Lanthanide chelates can be used for MRI and optical imaging. The near term goals are to design better smart agents and to incorporate both diagnostics and therapeutics into one agent. Difficulties exist in moving the diagnostic methods into the clinic, the development of screening techniques, the enhancement of MRI signal to noise, the identification of new mechanisms for inherently targeted agents, and molecule internalization (intracellular versus extracellular) for smart agent development. An interdisciplinary approach is vital for advancing this field.

A Human/Mouse Integrative Approach to Cancer Research [Presentation Slides]
The goals of the Mouse Models of Human Cancer Consortium (MMHCC) are to develop innovative modeling and phenotyping, credential mouse models for how well they inform human translational research, apply mouse models for discovering and testing new therapy, prevention, early detection and imaging strategies and communicate outcomes to the cancer research community

The ideal mouse model depends upon the question(s) being asked. Cancer models databases, enterprise vocabulary services and several supporting technologies are available through the MMHCC. Additional information can be found at http://emice.nci.nih.gov .

Panel – Preclinical Development: Addressing the Challenges
Issues raised by the panel:

- Can we humanize mice, rabbits, dogs, armadillos, etc.? The answer depends on the compound and whether certain animal models are being used to answer questions for a particular compound. There may be no appropriate animal model in certain instances. Investigator should know if target antigen is expressed in the animal model. In addition to a mouse information repository, a woodchuck liver cancer model exists.
- Is the xenograft or non-xenograft more predictive of human response? The xenograft model excludes T-cell response, a significant variable. What about the athymic vs. transgenic mouse model? It was noted that tumors grow spontaneously in the transgenic model.
- Toxicity tests must be performed in two species (one rodent model and another non-rodent model) since human extrapolation is more likely seen in two species rather than one. One species may be acceptable to the FDA if the receptor binder is the exact metabolite in humans and information to support one species is deemed adequate by the FDA.
- What about efficacy testing in humans first, assuming that safety data is complete? Animal models are often not representative of clinical reality.
- An unequal playing field exists among drugs, biologics and devices, e.g. contrast agents are used off label and have more risk than radiopharmaceuticals.

Imaging Devices: The Needs, Problems and Challenges [Presentation Slides]
Examples of mega trends that affect the medical imaging device industry:

- Industry consolidation leading to increased average size of remaining companies and fewer competitors
- Increased markets for imaging devices
- Decrease in venture capital for medical device innovation
- Manpower shortage in radiology and related allied health fields
- Advent of some potentially disruptive technologies
- Compact, portable and inexpensive ultrasound equipment
- Radionuclide probes for specific targets
- PET-CT multimodality machines

Information technology, medical technology and scientific discovery were identified as forces of change, consumer empowerment.

The recommendations from the 2001 Institute of Medicine report on Developing New Technologies (Mammography and Beyond – Technology for Early Detection of Breast Cancer) aimed at improving the development and adoption processes for new technologies and making the most of technologies currently available were reviewed.

The National Institute of Standards and Technology's Advanced Technology Program (ATP) was also discussed. This ATP is aimed at high risk, high payoff technology development. The program requires a lead and co-investment from industry and covers a wide spectrum of technology in healthcare. The efforts in drug development aimed at cellular signals and physiological parameters were discussed. In silico biology simulation and modeling are used to select drug targets. Imaging is important in early phase drug studies on human subjects to screen for the desired effect and to eliminate candidate new molecular entities that will not find ultimate success. Quantitative image analysis will become widespread. The development of robust databases and the tools to gain additional information from clinical and scientific studies will develop rapidly. The infrastructure for fully electronic support of clinical trials is a high priority.

Conclusions:

- Change is imperative
- Government should facilitate and collaborate to orchestrate the change
- Information and simulation sciences will have central role
- Very different and better models for sponsorship and regulation of technology development are needed.

Comparison of Models for Imaging Angiogenesis

Information on the use of ultrasound and MRI for measuring flow and perfusion of tumors was presented. Ultrasound techniques can be correlated with histology in calibrated phantoms. Studies are currently underway to calibrate in vivo and correlate with therapeutics. Initial studies with MRI indicate a link between kinetics and response to therapy.

Major needs:

- Correlative studies with new therapeutics
- Ultrasound needs to improve system bandwidth and develop agents with restricted range of diameters
- Macromolecular contrast agent development for MRI as well as more rapid acquisition
- Further development of Multi-modality platforms

Several new agents for ultrasound and MRI imaging of various aspects of angiogenesis were discussed. Ultrasound appears to have a role in the progress made towards imaging flow and vascular density. Targeted contrast agents have succeeded in vivo.

Current In Vitro Imaging Capabilities

"The Cellular Observatory", a new and unique facility at the Pacific Northwest National Laboratories (PNNL) was developed to obtain real-time data on the function of living cells, cultures and tissues. Areas of development include:

- The combination of simultaneous probing of single protein conformational motions with enzymatic reaction turnovers and optical imaging techniques that produce 20-30 nm spatial resolution for measurements of chemical interactions within cells
- New microscopy with coherent antistokes raman scattering combined with two photon confocal imaging methods for imaging internal and external structures of cells and changes over time
- Magnetic Resonance Microscopy (MRM) capabilities combined with ultraslow magnetic angle spinning for cell, tissue and animal studies
- MRM of cells combined with dynamic nuclear polarization
- 3D MR images of rats to define the complex architecture of the upper respiratory tract in computational models employed for inhalation toxicology
- Spatially resolved low radiation dose research to observe cells under controlled stressful conditions

Optical Imaging [Presentation Slides]

Optical imaging represents one of the biggest growth areas in medical imaging. The most important optical imaging modalities for in vivo studies are optical coherence tomography and photon migration spectroscopy. Sensing probes such as near-infrared fluorescence (NIRF) probes, long-circulating NIRF probes and DOT imaging systems, are available for optical imaging. The challenges for improving optical imaging are:

- Can we acquire tomographic/3D image data sets in vivo?
- How deep can we see with optical imaging?
- How can the measurements be made quantitative?
- Can this technology be developed into a clinical method?

Magnetic Resonance Spectroscopy
Non-invasive, quantitative measurement of small/mobile molecules can be performed with magnetic resonance spectroscopy (MRS). MRS requires mM concentrations and is performed in conjunction with high resolution anatomic imaging, MRI. Either single voxel or spectroscopic image data can be obtained.

Molecular imaging of F19 with spectroscopy is associated with gene therapy, metabolic imaging of protons in prostate cancer and metabolic imaging of P31 in non-Hodgkin's lymphoma.

The challenges for magnetic resonance spectroscopy:

- Sensitivity – which will require higher field strength systems and better RF coils
- Spectral quality – that can be improved with lipid/water suppression software, high field strength systems and automated, fast shimming
- Robust routine operation can be achieved with "tech friendly" data acquisition and refinements in data analysis
- Multi-nuclear capability will require broad-band, 2^{nd} RF channels, H1 decoupling and polarization transfer
- Translation – preclinical to clinical and across platforms.

Hybrid Machines [Presentation Slides]
The first clinical images from the PET/CT machine at the University of Pittsburgh were made in May 2001, and over 300 patients with various cancers have been studied since then. The machine has had a significant impact on the management of patients undergoing radiation therapy. The machine defined the biologic target volumes and improved the treatment efficacy by:

- Increasing the radiation fields to include additional lesions
- Boosting tumor dose while sparing normal tissue
- Up-staging patients avoiding ineffective treatments
- Monitoring treatment response

Great strides in the future design and performance of this machine will be achieved in the next few years. In the future, quantitative whole body imaging will take five minutes or less.

Imaging Guided Radiation Planning and Treatment
Inverse planning can be performed by specifying the beam and dose distribution. This means dose painting or sculpturing is now possible. However, the big question is how much to paint or sculpt, in other words the dose and volume to be treated. Biological images can assist in this by defining the tumor extent and burden, estimating the radiosensitivity of the target, and avoiding normal tissue.

The future will entail multi-modality cancer therapy, giving treatment in the manner that conforms to the disease in its multiple dimensions: anatomical, stage, radio/chemo sensitivity, based on probability of metastases and several other measures.

Panel – Devices: Addressing the Challenges
Dilemmas discussed by the panel:

- Tradeoffs exist between resolution and sensitivity; one exists at the expense of the other in human imaging.
- Radiation dose issues come into play when performing repetitive imaging studies.
- Can development costs be reduced? Animal studies are less costly than human studies. PET, SPECT and MR have huge development costs.
- Small market size impedes development. A device without an established market, not geared towards commercial development, is deemed a risky investment.
- Genomics and proteomics need to be correlated with images.
- What is the ultimate market for small animal imagers? Should NCI be in the business of developing this technology rather than distribution? Could animal imaging equipment become a shared resource like super computer centers?

-
- Multi-modalities are emerging, e.g. optical methods with MR.
- A strategy for simultaneous regulatory approval for both probe and device would be to communicate early with the FDA, perhaps submit a letter of intent to the Interagency Council on Biomedical Imaging in Oncology (http://www3.cancer.gov/scienceresources/announcements/imaging.html).
- A problem exists in the MR research community when a researcher has the equipment, contrast agents, therapeutic and imaging process, but industry is not interested in all aspects. The possibility of intellectual property issues being handled in the NIH research grant setting was discussed. Investigators through the NCI MMHCC can purchase mice pairs with no restrictions on usage. Shared knowledge amongst investigators is in the form of publications.
- Additional questions of population, comparativeness, efficacy and effectiveness that are not directly related to regulatory issues might suit coverage approval.
- PET manufacturers almost went out of business. One problem was the lack of clinical trials. Conditional coverage by CMS and third party would be a big help in acquiring clinical trial data for new devices.
- There are outcomes of clinical importance before survival. It may not be necessary to go all the way out for diagnosis.
- There are different cultural attitudes for clinical studies. The clinical radiologist and physician formulate patient treatment options, but the ultimate treatment decision resides with the patient.
- PET reimbursement will be considered on a cancer by cancer and indication by indication basis. It was stated that CMS needs to take a step back and rethink doing clinical studies and new ideas for obtaining standardization in imaging. How can NCI help in that process?
- There needs to be improved communication between device and pharmaceutical industries.

Summary [Presentation Slides]

Oncologic imaging has evolved from determining size and morphology to studying physiological parameters of metabolism, angiogenesis and other functions to ultimately determining molecular pathways. Three types of innovation exist: the development of new technology, distribution of imaging technology, and improvement of current technologies.

Challenges in current biomedical imaging development:

- Standardization, quantification and visualization
- Lack of intermodality comparison
- Validation as biological or surrogate markers
- Regulatory limitations and other perceived roadblocks

Imaging continues to evolve and is becoming integral to diagnostic and therapeutic medical care. Continued funding support, intensified communication and collaboration among the regulatory, research, funding and medical environments are crucial for the successful development of devices and probes.